UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 12 1988

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDOM

SUBJECT: 2,4-D, Butoxyethyl ester; Review of Acute Studies

TO: Richard Mountford PM-23
Registration Division (TS-767)

FROM: Robert P. Zendzian PhD
Senior Pharmacologist
Toxicology Branch
HED (TS-769)

THROUGH: William Burnam
Deputy Chief
Toxicology Branch

Compound; 2,4-D butoxyethyl ester

Tox Chem #315A

Registration #464-513 Registrant; not given

MRID # 405157-01-06 Tox Project #8-0956

Action requested

Review the following acute toxicity studies on the butoxyethyl ester of 2,4-D;

MRID 406298-01
2,4-D, Butoxyethyl Ester, technical: acute oral toxicity study in Fischer 344 rats, Jeffrey, M.M, Battles, J.E. & Lomax, L.J. Mammalian and Environmental Toxicology Research Laboratory, DOW Chemical Co. Laboratory Project Study ID K-007722-006A, Apr 22, 1987.

MRID 405298-02
2,4-D, Butoxyethyl Ester, technical: acute dermal toxicity study in New Zealand White rabits, Jeffrey, M.M, Battles, J.E. & Zimmer, M.A., Mammalian and Environmental Toxicology Research Laboratory, DOW Chemical Co. Laboratory Project Study ID K-007722-006D, July 8, 1987.

MRID 406298-03
2,4-D, Butoxyethyl Ester, technical: acute aerosol inhalation study in Fischer 344 rats, Streeter, C.M., Battles, J.E. & Yano, B.L. Mammalian and Environmental Toxicology Research Laboratory, DOW Chemical Co. Laboratory Project Study ID K-007722-007, Sept 16, 1987.

MRID 406298-04
2,4-D, Butoxyethyl Ester, technical: primary eye irritaion study in New Zealand White rabbits, Jeffrey, M.M, Mammalian and Environmental Toxicology Research Laboratory, DOW Chemical Co. Laboratory Project Study ID K-007722-006C, July 8, 1987.

MRID 406298-05
2,4-D, Butoxyethyl Ester, technical: primary dermal irritation study in New Zealand White rabits, Jeffrey, M.M, Mammalian and Environmental Toxicology Research Laboratory, DOW Chemical Co. Laboratory Project Study ID K-007722-006B, July 8, 1987.

MRID 406298-06
Butoxyethyl 2,4-dichlorophenoxyacetate, dermal sensitization potential in Hartly strain guinea pigs. Jeffrey, M.M, Mammalian and Environmental Toxicology Research Laboratory, DOW Chemical Co. Laboratory Project Study ID K-007722-005, July 8, 1987.

TRID 470141-014
2,4-D Butoxyethyl ester; dermal sensitization potential in the guinea pig, Carreon, R.E., Mammalian and Environmental Toxicology Research Laboratory, DOW, July 22, 1985.

TRID 470136-030
Delayed Contact hypersensitivity study in guinea pigs of AGR 218503 2,4-D Butoxyethyl seter for DOW Chemical USA, Buehler, E.V. Hill Top Research,, No 85-1197-21, Nov 21, 1985.

Conclusions

MRID 406298-01. The acute oral LD_{50} of 2,4-D, butoxyethyl ester was 866 mg/kg in male and female Fischer 344 rats. Signs of toxicity consisted of nonspecific depression. Rats given 1500 mg/kg showed stomach erosions/ulcers at necropsy. Guideline. Toxicity Catagory III.

MRID 406298-02. The acute dermal LD_{50} of 2,4-D, butoxyethyl ester was >2000 mg/kg female and 1829 (1335-2002) mg/kg in male rabbits. In the males erythema was observed at 1000 and 2000 mg/kg but not at 200 mg/kg. Guideline. Toxicity catagory III

MRID 406298-03. Two of five Male Fischer 344 rats exposed to 4.6 mg/L 2,4-D, Butoxyethyl Ester for four hours died. All females survived. LC_{50} >4.6 mg/L. Guideline. Toxicity catagory III.

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MRID 406298-04. Instillation of 0.1 ml of technical 2,4-D, Butoxyethyl Ester in the right mye of six NZW rabbits produced very mild signs of irritation which were resolved in 48 hours for four and 72 hours for the remaining one. Guideline. Toxicity Catagory III

MRID 406298-05. Application of 0.5 ml 2,4-D, Butoxyethyl Ester to the shaved back of NZW rabbits produced very slight erythremia which cleared in 72 hours. Guideline. Toxicity catagory III.

MRID 406298-05. Butoxyethyl 2,4-dichlorophenoxyacetate was not a dermal sensitizer in guinea pigs under the test conditions (modified Buehler Method).

TRID 470141-014. Butoxyethyl 2,4-dichlorophenoxyacetate was a dermal sensitizer in guinea pigs under the test conditions (modified Buehler Method).

TRID 470136-030. Butoxyethyl 2,4-dichlorophenoxyacetate was a dermal sensitizer in guinea pigs under the test conditions (modified Maguire Method).

Attachments

DERs
One-liner

Data Evaluation Report

Compound 2,4-D, Butoxyethyl ester

Citation 2,4-D, Butoxyethyl Ester, technical: acute oral toxicity study in Fischer 344 rats, Jeffrey, M.M, Battles, J.E. & Lomax, L.J. Mammalian and Environmental Toxicology Research Laboratory, DOW Chemical Co. Laboratory Project Study ID K-007722-006A, Apr 22, 1987, MRID ~~405157-01~~, 406295-01

Reviewed by Robert P. Zendzian Ph.D
Senior Pharmacologist

Core Classification Guideline

Conclusions

The acute oral LD_{50} of 2,4-D, butoxyethyl ester was 866 mg/kg in male and female Fischer 344 rats. Signs of toxicity consisted of nonspecific depression. Rats given 1500 mg/kg showed stomach erosions/ulcers at necropsy. Toxicity Catagory III.

Materials

2,4-D, butoxyethyl ester

Sample Reference:	AGR 218503
CAS Number:	001929-73-3
Physical state:	Amber liquid
Assayed	96.0% 2,4-D-BE

Eight-week old Fischer 344 rats from Charles River, Kingston

Experimental Design

"Five rats per sex received 100, 500 or 1500 mg/kg of the test material per kg body weight by single dose gravage. The test material was administered in 15% (v/v) solution in corn oil." Animals were examined daily and weighed on the day of treatment and days 1, 7 and 14 post treatment. Animals that died on study or were sacrificed at termination were necropsied.

Results

No deaths occured at 100 and 500 mg/kg. All males and all females at 1500 mg/kg died within 48 hours of treatment. "Clinical observations included lethargy and lack of coordination when attempting to move, palpebral closure, lacrimation, chromodacryorrhea, facial/perineal soiling, diarrhea, labored respiration and unconsciousness in rats given 500 or 1500 mg/kg. Rats given 100 mg/kg were in apparent good health and survivors of all dose groups gained weight throughout the observation period. At necropsy, most rats given 1500 mg/kg of 2,4-D butoxyethyl ester, technical, had gross observations of stomach erosions/ulcers with hemorrhage and/or hemoglobinuria."

Data Evaluation Report

Compound 2,4-D, Butoxyethyl ester

Citation 2,4-D, Butoxyethyl Ester, technical: acute dermal toxicity study in New Zealand White rabits, Jeffrey, M.M, Battles, J.E. & Zimmer, M.A., Mammalian and Environmental Toxicology Research Laboratory, DOW Chemical Co. Laboratory Project Study ID K-007722-006D, July 6, 1987, MRID ~~405157-02~~, 4 06 2 95-02

Reviewed by Robert P. Zendzian Ph.D
Senior Pharmacologist

Core Classification Guideline

Conclusions

The acute dermal LD_{50} of 2,4-D, butoxyethyl ester was >2000 mg/kg female and 1829 (1335-2002) mg/kg in male rabbits. In the males erythema was observed at 1000 and 2000 mg/kg but not at 200 mg/kg. Toxicity catagory III

Materials

2,4-D, butoxyethyl ester

Sample Reference:	AGR 218503
CAS Number:	001929-73-3
Physical state:	Amber liquid
Assayed	96.0% 2,4-D-BE

New Zealand White rabbits, 2.6-3.3 kg from Hazleton Dutchland

Experimental Design

Animals were shaved and 24 hour later 5 males and 5 females were dosed dermally with 2000 mg/kg. After males in the high dose group died, two groups of 5 males were dosed with 200 and 1000 mg/kg. The application site was covered with a gauze dressing and a plastic wrap. After 24 hours the site was washed with mild soap and water and examined for dermal irritation. Animals were examined daily for two weeks post-dose and weighed on the day of treatment and 1, 7 and 14 days after dosing. Necropsy was performed on all animals that died and were sacrificed at termination.

Results

All females tested showed erythema at the application site but no other signs of toxicity.

Three males dosed at 2000 mg/kg died, on days 2, 4 and 5. All males at 1000 and 2000 mg/kg showed erythema at the application site and one male at 2000 showed edema. All males at 200 mg/kg remained normal.

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Data Evaluation Report

Compound 2,4-D, Butoxyethyl ester

Citation 2,4-D, Butoxyethyl Ester, technical: acute aerosol inhalation study in Fischer 344 rats, Streeter, C.M., Battles, J.E. & Yano, B.L. Mammalian and Environmental Toxicology Research Laboratory, DCW Chemical Co. Laboratory Project Study ID K-007722-007, Sept 16, 1987, MRID ~~405157-03~~, 41653502

Reviewed by Robert P. Zendzian Ph.D
Senior Pharmacologist

Core Classification Guideline

Conclusions

Two of five Male Fischer 344 rats exposed to 4.6 mg/L 2,4-D, Butoxyethyl Ester for four hours died. All females survived. LC_{50} >4.6 mg/L. Toxicity catagory III.

Materials

2,4-D, butoxyethyl ester

Sample Reference:	AGR 218503
CAS Number:	1929-73-3
Physical state:	Amber liquid
Assayed	96.0% 2,4-D-BE

Six-week old Fischer 344 rats from Charles River, Kingston

Experimental Design

"Whole-body exposures were conducted in a 112 liter glass and stainless steel Rochester-type chambers under dynamic airflow conditions." "Aerosols were generated by metering test material with an FMI pump ---- into a 1/4 J spray nozzle ---- where it was mixed with compressed air and sprayed into the chamber." "The partical size data were determined gravometrically during exposure from an aerosol sample collected with a cascade impactor--" Five male and five female rats "were exposed for a single four-hour duration, to a stable aerosol concentration of this formulation targeted to be the highest atainable. Chamber concentrations were gravimetrically determined six times from aerosol samples collected from the animal breathing zone---"

"Animals were observed for exposure-related effects during exposure, and daily during a two-week post-exposure period." Animals were weighed before exposure and on test days 2, 4, 9, 11 and 15. All animals that died on test and those remaining at terminal sacrifice were subject to gross necropsy.

Results

"(R)ats were exposed to a TWA concentration of 4.6 mg/liter 2,4-D butoxyethyl ester for four hours ---; this concentration was the highest attainable. The mass mean aerodynamic diameter (MMAD) of the aerosol was 3.03u and the geometric standard deviation — of the partical size distribution was 2.11 ——. The nominal exposure concentration was 10.1 mg/liter."

Two males died on day six. During exposure rats were soaked with test material and were observed to squint, lacrimate and salivate.

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Data Evaluation Report

Compound 2,4-D, Butoxyethyl ester

Citation 2,4-D, Butoxyethyl Ester, technical: primary eye irritaion study in New Zealand White rabits, Jeffrey, M.M, Mammalian and Environmental Toxicology Research Laboratory, DOW Chemical Co. Laboratory Project Study ID K-007722-006C, July 8, 1987, MRID ~~405157-04~~, 406598-01

Reviewed by Robert P. Zendzian Ph.D
Senior Pharmacologist

Core Classification Guideline

Conclusions

Instillation of 0.1 ml of technical 2,4-D, Butoxyethyl Ester in the right eye of six NZW rabbits produced very mild signs of irritation which were resolved in 48 hours for four and 72 hours for the remaining one. Toxzicity Catagory III

Materials

2,4-D, butoxyethyl ester

Sample Reference:	AGR 218503
CAS Number:	1929-73-3
Physical state:	Amber liquid
Assayed	96.0% 2,4-D-BE

New Zealand White rabbits, 3.0-3.3 kg from Hazleton Dutchland

Experimental Design

"The eyes of six adult New Zealand White rabbits were examined with 5% aqueous flourescein stain and established as being free of defects/irritation within twenty-four hours prior to study initiation. A 0.1 ml aliqout of the test material was instilled into the conjjunctival sac of the right eye of three male and three female rabbits. The left eye remained untreated and served as a control. The eyes of all rabbits remained unwashed. The behavior of each rabbit was observed immediately post-treatment for indicators of pain or discomfort. Both eyes of rabbits were examined with penlight at 1, 24, 48 and 72 hours post-instillation for conjunctival redness and chemosis, discharge, corneal opacity and reddening of the iris. The study was terminated 72 hours post-treatment and all animals humanely euthanatized."

Results

Very mild signs of irritation in all animals were resolved in five at 48 hours and the remaining one at 72 hours.

Data Evaluation Report

Compound 2,4-D, Butoxyethyl ester

Citation 2,4-D, Butoxyethyl Ester, technical: primary dermal irritation study in New Zealand White rabits, Jeffrey, M.M, Mammalian and Environmental Toxicology Research Laboratory, DOW Chemical Co. Laboratory Project Study ID K-007722-006B, July 8, 1987, MRID ~~405157-05,~~ 4 56 1 4 8 - 0 1

Reviewed by Robert P. Zendzian Ph.D 7/5/83
Senior Pharmacologist

Core Classification Guideline

Conclusions

Application of 0.5 ml 2,4-D, Butoxyethyl Ester to the shaved back of NZW rabbits produced very slight erythremia which cleared in 72 hours. Toxicity catagory III.

Materials

2,4-D, butoxyethyl ester

Sample Reference:	AGR 218503
CAS Number:	1929-73-3
Physical state:	Amber liquid
Assayed	96.0% 2,4-D-BE

New Zealand White rabbits, 2.6-3.3 kg from Hazleton Dutchland

Experimental Design

"Twenty-four hours prior to study initiation, approximately 10 cm^2 of the back of six New Zealand White rabbits was clipped free of fur. A 0.5 ml aliquot of the test material was applied to the back under a 2.5 cm^2 gauze patch and held in place with non-irritating tape. The gauze patch was covered with a flannel bandage taped to the rabbit." "The wrapping and gauze patch were removed after four hours. The back was wiped with a damp disposable towel to remove any residual test substance. The application site were graded for erythema, edema and necrosis within thirty minutes and 24, 48 and 72 hours after patch removal. The study was terminated 72 hours post-treatment and all animals humanely euthanized."

Results

Very slight erythema waa observed on all animals following exposure. All application sites had cleared at 72 hours.

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Data Evaluation Report

Compound 2,4-D, Butoxyethyl ester

Citation Butoxyethyl 2,4-dichlorophenoxyacetate, dermal sensitization potential in Hartly strain guinea pigs. Jeffrey, M.M, Mammalian and Environmental Toxicology Research Laboratory, DOW Chemical Co. Laboratory Project Study ID K-007722-005, July 8, 1987, MRID 40515706, 40515706

Reviewed by Robert P. Zendzian Ph.D 2/5/88
Senior Pharmacologist

Core Classification Minimum

Conclusions

Butoxyethyl 2,4-dichlorophenoxyacetate was not a dermal sensitizer in guinea pigs under the test conditions (modified Buehler Method).

Materials

2,4-D, butoxyethyl ester

Sample Reference:	ACPR 86-32
Physical state:	liquid
pH:	3.8
Assayed	97.5% 2,4-D-BE

Male Hartly albino guinea pigs from Charles River, Kingston.

Experimental Design

The test was described as a modification of the Buehler Method.

Backs of guinea pigs were clipped 24 hours prior to start of the study. Undiluted test material, 0.4 ml, was applied, in Hill Top chambers, to the left side of the back of 10 animals. A 0.1% solution of the positive control, 1-chloro-2,4-dinitrobenzene (DNCB), was similarly applied to 10 additional animals. The exposure period was six hours, once a week for a total of three applications. Two weeks after the last application, the backs were again clipped and the test material or DNCB was applied to the right side of the respective animals. Application sites were observed and scored 24 and 48 hours after the challenge dose. "The test material was considered a potential human skin sensitizer if a positive response indicative of sensitization (erythema and/or edema) was observed on two or more animals out of a total of ten animals tested."

Results

No response to challange with the test compound was observed. Two of the 10 animals treated with the positive control, DNCB, showed a positive response to challenge with a score of 2 (moderate) erythema 48 hours after challenge.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 1 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Registration No. 464-518
2,4-D Butoxyethyl ester

FROM: Mary L. Waller
Technical Support Section
Fungicide-Herbicide Branch
Registration Division (TS-767C)

mlw 4/10 — 4/10 '86

TO: Richard Mountfort, PM 23
Fungicide-Herbicide Branch
Registration Division (TS-767C)

APPLICANT: Dow Chemical U.S.A.
P.O. Box 1706
Midland, MI 48640

ACTIVE INGREDIENT:
2,4-Dichlorophenoxyacetic Acid, Butoxyethyl Ester . . . 96%
INERT INGREDIENTS: 4%

BACKGROUND:

The registrant has submitted two dermal sensitization studies. One study (Accession Number 261358) was conducted by Dow Mammalian and Environmental Toxicology Research Laboratory. The other study (Accession Number 261284) was conducted by Hilltop Research, Inc. The method of support was not indicated.

RECOMMENDATION:

FHB/TSS finds the studies acceptable to support registration and classifies the product as a sensitizer.

The Product Manager should inform the registrant that when conducting future dermal sensitization studies, individual skin irritation scores for erythema and edema should be provided after each induction and challenge treatment.

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LABELING:

Add the following sentence: This product may cause allergic skin reactions.

REVIEW:

(1) Dermal Sensitization Study: Dow Mammalian and Environmental Toxicology Research Laboratory; Accession Number 261358; July 22, 1985.

PROCEDURE:

Twenty male Hartley albino guinea pigs were shaved on the back and 24 hours later, 10 animals per group were treated with 4 applications within 10 days with either 0.1 ml of undiluted test material or DER 331 epoxy resin (a known sensitizer) as a 10 percent solution in Dowanol DPM/TWEEN 80. Each insult treatment was applied to a patch which was placed on the test site on the animal's back. The first and second insult treatments were kept under occlusive wrap for 24 hours. The third and fourth insult treatments were kept under occlusive wrap for 48 hours. At the third treatment, each animal also received a total of 0.2 ml of Freund's Complete Adjuvant which was injected intradermally adjacent to the test site. After 2 weeks, the animals' flanks were shaved and challenged. Skin irritation was scored during insult and challenge phase.

RESULTS:

No skin irritation was noted in either group during the insult phase. After challenge dose, the test group exhibited erythema (hyperemia) ranging from slight to moderate and the positive control group exhibited moderate to marked erythema.

STUDY CLASSIFICATION: Core Guideline Data.

TOXICITY CATEGORY: Sensitizer.

(2) Dermal Sensitization Study: Hill Top Research, Inc.; Project No. 85-1197-21; Accession No. 261284; November 21, 1985.

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PROCEDURE:

Ten male and ten female Hartley albino guinea pigs were exposed for 6 hours once a week for 3 weeks to 0.3 ml of test material applied to a shaven test site under occlusive wrap on the animals' backs. After 2 weeks, 0.3 ml of 50 percent w/v formulation of test material in acetone was applied to a new test site under occlusive wrap on the animals' backs. A naive control group consisting of five males and five females received the same challenge treatment. All animals were restrained for 6 hours after exposure. Skin irritation was scored after challenge treatment.

RESULTS:

After challenge treatment, the naive control group exhibited no skin irritation and 13/20 animals in the test group exhibited trace irritation (scores < 1).

STUDY CLASSIFICATION: Core Minimum Data - See comments under Recommendation.

TOXICITY CATEGORY: Sensitizer.

END